RAC Review of Protocol #0107-488
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My questions and comments about this protocol focus on its ethical aspects, primarily safety, the harm-benefit balance, and consent issues (the consent form and process). However, as a nonscientist I am ill-equipped to address the safety issues; I rely upon the scientific reviewers' evaluations, and ask the investigator's indulgence if my questions are overly naive.

This protocol proposes to use an HIV-based lentiviral vector containing an anti-HIV antisense sequence that targets the HIV envelope gene, and that should in theory destroy wild-type HIV. The protocol materials emphasize that this is a phase I safety study and that, if everything works as it is supposed to, only in the highest dosing cohort could the effect be sufficient to meaningfully reduce viral load.

1. Clarification of the study population and the alternatives available to these subjects would be helpful.

These clarifications should be appropriately included in the consent form, which in its draft form does not do an adequate job of presenting this information.

The protocol materials state that subjects must have been on HAART which has failed them, or must be resistant to HAART, or must have discontinued HAART. The protocol states that these potential subjects have "no treatment alternatives" and a very poor prognosis. However, the consent form states, in several places, that those who choose not to enroll, or who withdraw from participation, will be able to receive standard treatment. What "standard treatment" means for these potential subjects should be clarified, and treatment failure, resistance, or discontinuation should be included in the "Invitation to participate", which currently says only "You...are HIV positive." Moreover, any voluntary discontinuation must predate the potential subject's receiving any information about the study, so that the prospect of not having to follow a rigorous HAART regimen but still receive "treatment" is not misleadingly permitted to be a factor in a potential subject's decision to enroll in this phase I study. Finally, I would like more information about subject recruitment and the consent process, to address my concerns about the information given to potential subjects about the limitations of participating in a phase I study. The prospect of subjects' going without any antiretroviral therapy for the expected 6 months of study participation raises safety concerns that the investigator should address in more detail.

2. Two related questions have to do with the dose escalation design. First, I would like the investigator to explain the safety justifications for the dose levels selected, and their relationship to the preclinical safety dosing. Second, if it is indeed the case, as stated in the protocol materials, that only at the highest dose could efficacy be seen under the best of circumstances, the consent form should clearly so state. Subjects entering a phase I study should be well-prepared to expect no efficacy at any dose, but if the first dose levels are not anticipated to be able to show any efficacy, saying so will help subjects to understand the real meaning of enrolling in a phase I study. Thus, I would like the investigator to say more about the anticipated harm-benefit balance for each

dosing cohort. And I would recommend a cohort-specific consent form and process. Phase I studies enrolling subjects with a serious disease always present ethical challenges, because of the high levels of risk to subjects if there is no efficacy, combined with the fact that efficacy is not a primary study endpoint at this stage, and with the fact that the subjects, however altruistic, may be primarily motivated by hope of benefit. Because of these challenges to decisionmaking, at minimum more information is needed.

3. The protocol states that there will be no DSMB for this study. Nonetheless, given the degree of risk presented by the 6 months without antiretroviral therapy, a monitoring plan seems clearly needed. Arguably, data and safety monitoring should be carried out by someone other than the investigator. Thus, I would like the investigator to describe the data and safety monitoring plan.

4. Although my understanding of lentiviral vectors is limited, I have some concerns about their safety and the amount of preclinical data available. I imagine that the investigator will be addressing those concerns in his responses to the scientific reviewers. I would like the investigator to summarize his responses to those concerns for me, by explaining why he believes it is ethically appropriate to move from preclinical to clinical studies at this time and via this design.

5. Each of the above questions has implications for the consent form and process, and I would expect the investigator to draft appropriate modifications to the consent form in accordance with his responses. In addition, I have a number of other comments and suggestions about the draft consent form submitted, which I would like the investigator to consider and present to his IRB:

Vocabulary appropriate to a phase I study: The term "patient", when used to describe study subjects, should be replaced with "subject" or "patient-subject". The term "treatment", or "investigational treatment", when used to describe the experimental intervention, should be replaced with "experimental intervention" or a related term. And although the consent form usually describes blood cells as being "transduced with" the construct, there are a few places where "treated with" is misleadingly used instead. (A term more accessible to nonscientists, like "exposed to" or "infected with" could also be used throughout, instead of "transduced with".) All of these changes are intended to minimize the impression given that the study intervention is a successful treatment, which it is not.

Purpose section: This important section of the consent form seems to overstate the potential benefits of study participation and to misstate the purpose of this phase I study. I think it needs to be rewritten, to emphasize the safety endpoint and to deemphasize the efficacy endpoint. I'm confident that the investigator can accomplish this easily, but would be glad to provide some more specific suggestions if he plans to revise before submitting to his IRB and would like assistance.

Definition and explanation of construct: I couldn't find anyplace in the consent form where "VRX496" is defined or explained. Nor could I find any mention that this study involves gene transfer research. An explanation of the nature of the transgene, construct, and gene transfer intervention should be provided.

Risks of harm from the construct: There is nothing in the risk statement addressing commonly addressed concerns regarding transgenes and vectors, including germline integration and insertional mutagenesis – which, as I understand it, may be genuine issues with lentiviral vectors. Appropriate risk information about VRK496 should be added.

Vague and overoptimistic benefits section: Here I will propose revised text for the investigator's consideration. The suggested changes are meant to emphasize limitations on any expectation of benefit in this phase I study. The investigator is of course free to disagree and provide his own revision.

"Because this is a phase I study of an experimental intervention that has never been tested in humans before, no direct benefits can be expected for subjects. The purpose of this study is to find the highest safe dose of VRX496. If VRX496 is able to reduce the amount of HIV infection, and if a subject receives a large enough dose of VRX496 to make a difference, then it is possible that some subjects at the highest dose level could have better CD4 counts temporarily than they would have if they did not participate in the study. However, the main benefit from this study will be to future patients, if it leads to better treatment for patients with HIV infection. The chance of benefit for any subject in this study is very probably low or none."